TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney's Docket Number: 02481.1603

U.S. Application No.: 09/101672

International Application. No.	International Filing Date	Priority Date Claimed
PCT/EP97/01167	March 07, 1997	March 20, 1996

Title of Invention:

PREPARATION CONTAINING A COMBINATION OF 5-METHYLISOXAZOLE-4-CARBOXYLIC ACID-(4-TRIFLUOROMETHYL)-ANILIDE AND N-(4-TRIFLUOROMETHYLPHENYL)2-CYANO-3-HYDROXYCROTONIC ACID AMIDE

Applicants For DO/EO/US:

Robert BARTLETT and Johann THEN

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes (Amended Sheets) to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:
    a. [ ] Verified Small Entity Statement.
    b. [ ] Annexes (Amended Sheets) to Intl. Preliminary Examination report.

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
	PCT/EP97/01167	02481.1603

17. [X] The following fees are submitted: | CALCULATIONS

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO.....$930.00

International preliminary examination fee paid to USPTO (37 CFR 1.482).....$720.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$790.00

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,070.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....$ 98.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $ 930.00

Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $

Claims	Number Filed	Number Extra	Rate	
Total Claims	18-20=		X $22.00	$
Independent Claims	4 - 3=	1	X $82.00	$ 82.00
Multiple dependent claim(s) (if applicable)			+$270.00	$

TOTAL OF ABOVE CALCULATIONS = $1012.00

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28) $

SUBTOTAL = $1012.00

Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). + $

TOTAL NATIONAL FEE = $1012.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property + **$**

TOTAL FEES ENCLOSED = $1012.00

Amount to be refunded $

charged $

a. [X] A check in the amount of **$1012.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

Ernest F. Chapman
Reg. No. 25,961

SEND ALL CORRESPONDENCE TO:
Finnegan, Henderson, Farabow Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

02481.1603
Submitted: July 15, 1998

PATENT
ATTORNEY DOCKET NO. 2481.1603-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re National Phase Application of
PCT/EP97/01167

Robert Bartlett et al.

Serial No.: 09/101,672) Art Unit:TO BE ASSIGNED

Filed: July 15, 1998) Examiner: TO BE ASSIGNED

For: PREPARATION CONTAINING A COMBINATION OF 5-METHYLISOXAZOLE-4-CARBOXYLIC ACID-(4-TRIFLUOROMETHYL)-ANILIDE AND N-(4-TRIFLUOROMETHYLPHENYL) 2-CYANO-3HYDROXYCROTONIC ACID AMIDE) **Box PCT**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

SUPPLEMENTAL PRELIMINARY AMENDMENT

Prior to the examination of the above-referenced application on the merits, please amend the application as follows:

IN THE CLAIMS:

Please amend claims 12, 20, 26, and 27 as follows:

12. A solid composition comprising:

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I

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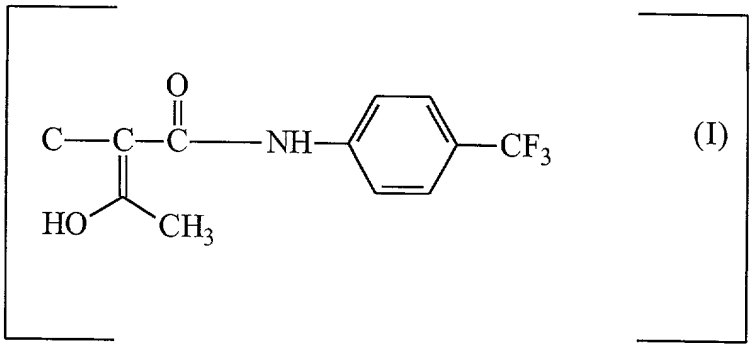

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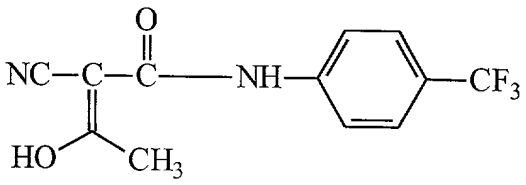

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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

20. A method of treating an immunological disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I

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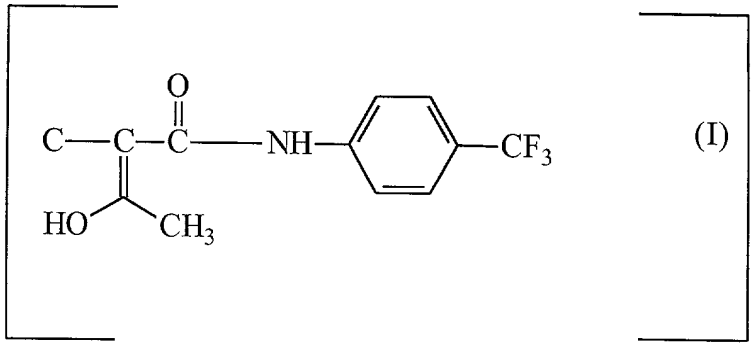

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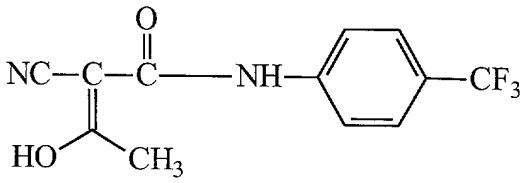

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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

26. A method of treating a disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I

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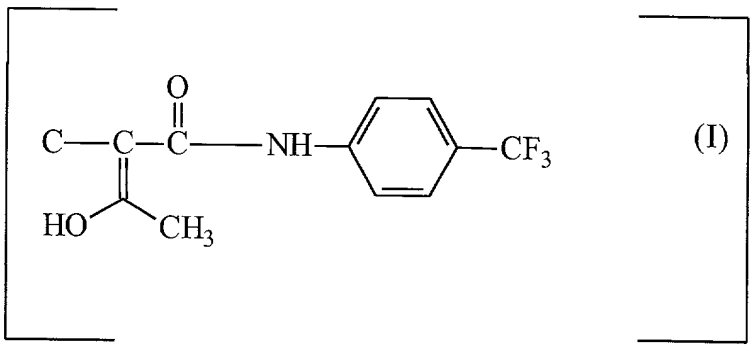

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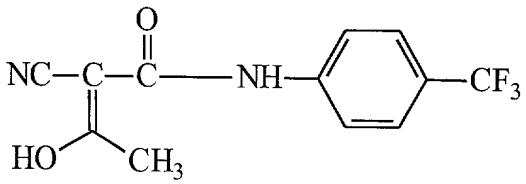

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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I;and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

27. A method of treating a cancerous disease comprising administering to a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I

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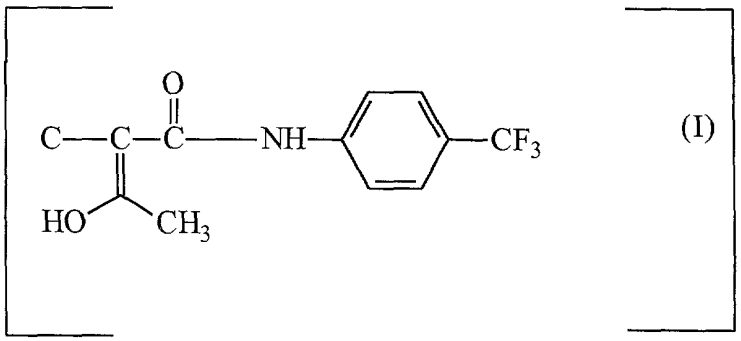

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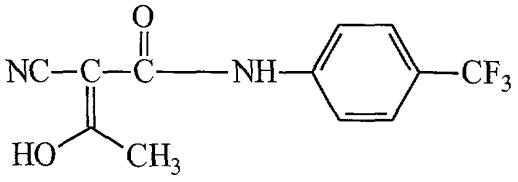

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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

REMARKS

Claims 12-29 are currently pending. Claims 12, 20, 26, and 27 have been amended to correct the printing error that occurred in the structural formula of formula I. Specifically, the cyano group that is alpha to the carbonyl moiety did not print correctly in the July 15, 1998 preliminary amendment. Support for this amendment can be found

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at page two of the specification. No new matter has been introduced by these amendments.

In view of the preceding amendments and remarks, it is submitted that pending claims 12-29 are in condition for allowance and a prompt Notice of Allowance is earnestly solicited.

It is believed that there are no additional fees due in connection with the filing of this response. However, if any such fees are due, including any fee for extension of time, the Commissioner is hereby authorized to charge such fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: _____

Allen Jensen
Reg. No. 28,224

Dated: August 17, 1998

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PATENT
ATTORNEY DOCKET NO. 2481.1603-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re National Phase Application of PCT/EP97/01167	
Robert Bartlett et al.	
Serial No.: TO BE ASSIGNED	Art Unit:TO BE ASSIGNED
Filed: Concurrently herewith	Examiner: TO BE ASSIGNED
For: PREPARATION CONTAINING A COMBINATION OF 5-METHYLISOXAZOLE-4-CARBOXYLIC ACID-(4-TRIFLUOROMETHYL)-ANILIDE AND N-(4-TRIFLUOROMETHYLPHENYL) 2-CYANO-3HYDROXYCROTONIC ACID AMIDE	**Box PCT**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above-referenced application on the merits, please amend the application as follows:

IN THE CLAIMS:

Please cancel claims 1-11.

Please add the following new claims:

--12. A solid composition comprising:

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

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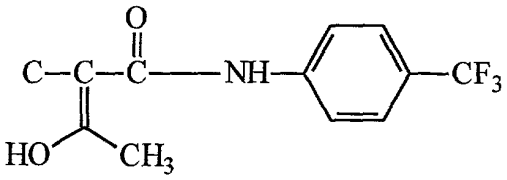
a second component comprising a compound of formula I



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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

13. The composition as claimed in claim 1, wherein concentration of the second component is from about 0.5% to about 20% of the first component.

14. The composition as claimed in claim 1, wherein the concentration of the second component is from about 0.8% to about 15% of the first component.

15. The composition as claimed in claim 1, wherein the concentration of the second component is from about 1% to about 10% of the first component.

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16. The composition as claimed in claim 1, wherein the concentration of the second component is from about 1% to about 5% of the first component.

17. The composition as claimed in claim 1, which comprises a first component and a second component in a form for rectal or oral administration.

18. The composition as claimed in claim 1, wherein the first component is separate from the second component, and the first and second components are of similar administration forms.

19. The composition as claimed in claim 1, wherein the first component is separate from the second component, and the first and second components are of different administration forms.

20. A method of treating an immunological disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

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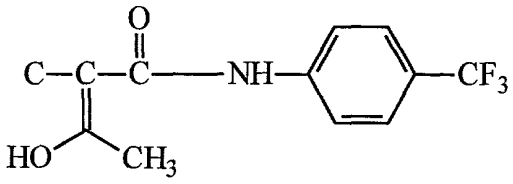
a second component comprising a compound of formula I



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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

21. The method of claim 20, wherein the composition produces a hyperadditive increase in the immunosuppressive effect.

22. A method according to claim 12, wherein the immunological disease is an acute immunological disease.

23. A method according to claim13, wherein the acute immunological disease is sepsis, allergy, graft-versus-host reaction, or host-versus-graft reactions.

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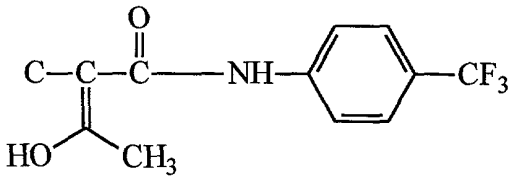
24. A method according to claim 12, wherein the immunological disease is an autoimmune disease.

25. A method according to claim 15, wherein the autoimmune disease is rheumatoid arthritis, systemic lupus erythrematosus, multiple sclerosis, psoriasis.

26. A method of treating a disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the

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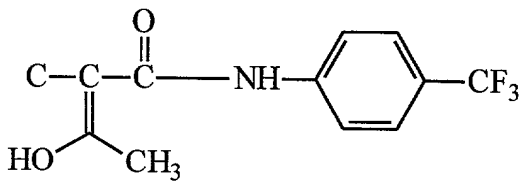
first component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

27. A method of treating a cancerous disease comprising administering to a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



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or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component.

28. A method according to claim 18, wherein the cancerous disease is lung cancer, leukemia, ovarian cancer, sarcoma, Kaposi's sarcoma, meningioma, intestinal

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cancer, lymph node cancer, brain tumors, breast cancer, pancreatic cancer, prostate cancer, or skin cancer.

29. A process for the preparation of a pharmaceutical composition of claim 1, which comprises processing components 1, 2, and 3 into a pharmaceutically acceptable form for administration.--

IN THE ABSTRACT:

Please delete the Abstract and insert therefor the Abstract set forth on the attached sheet.

REMARKS

Claims 1-11 have been cancelled and replaced by claims 12-29 to comport with U.S. practice and more particularly and distinctly claim what Applicant regards as his invention. No new matter has been introduced by these amendments.

In view of the preceding amendments and remarks, it is submitted that pending claims 12-29 are in condition for allowance and a prompt Notice of Allowance is earnestly solicited.

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It is believed that there are no additional fees due in connection with the filing of this response. However, if any such fees are due, including any fee for extension of time, the Commissioner is hereby authorized to charge such fees to our Deposit Account No. 06-916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Allen Jensen

Allen Jensen
Reg. No. 28,224

by
Carol P. Einaudi
Reg. No. 32,220

Dated: July 15, 1998

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ABSTRACT

A solid composition comprising 5-methyl-4'-trifluoromethyl-4-isoxazole carboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonic acid amide, suitable for treatment of immunological and cancerous diseases.

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Description

Combination preparation, comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide

The European Patent Application with the publication number 0 013 376 disclosed that 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide (compound 1) has antirheumatic, antiinflammatory, antipyretic and analgesic activity and can be employed against multiple sclerosis. Pharmaceuticals which comprise the active compound 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide are administered orally in doses of from 25 mg to 150 mg.

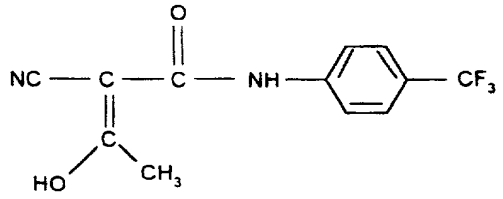
The European Patent Application with the publication number 0 217 206 reports that N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (compound 2) has immunomodulating properties and is suitable for treating chronic graft-versus-host disease and autoimmune diseases, in particular systemic lupus erythematosus. Pharmaceutical preparations which comprise a compound 1 or compound 2 can be administered in a dose of from 10 to 200 mg, preferably, however, of from 50 to 100 mg, in the case of an injection solution in ampoule form (intravenous), in particular based on compound 2 or a salt thereof, of from 1 to 30 mg, preferably of from 5 to 10 mg, and, in the case of rectal administration, of from 50 to 300 mg, preferably of from 100 to 200 mg. However, the oral administration of 5 mg or 10 mg of compound 1 or compound 2, in each case on its own, per kg does not have any significant effect.

It has been found that a combination preparation, which comprises compounds 1 and 2, exhibits surprisingly advantageous immunosuppressive effects. The addition of small quantities of compound 2 to the main active component compound 1 results in a marked increase in the activity of the combination preparation. Due to the magnitude of this effect, the use of this combination can be extended to areas which hitherto

remained closed to an immunosuppressive therapy using the individual components. Furthermore, the reduction in the dose, without any decreased activity, leads to greater safety in use. At the same time, it can be assumed that a reduction in the dose in association with unchanged activity will enable the therapy costs to be lowered substantially.

The invention relates, therefore, to a solid preparation which comprises component 1) 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide, component 2) N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide and/or a physiologically tolerated salt of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide and/or a stereoisomeric form of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide and
3) a pharmaceutical excipient,
wherein the content of component 1 is from 2 to 20 mg and the content of component 2) is from 0.3% to 50% of that of component 1).

The compounds 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide can be produced using known methods (EP 0 529 500). N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide having the following structural formula



is employed as such and/or a physiologically tolerated salt of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide and/or a stereoisomeric form of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide in the preparation according to the present invention.

Examples of suitable physiologically tolerated salts of N-(4-

trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide are alkali metal, alkaline earth metal or ammonium salts, including those of physiologically tolerated organic ammonium bases.

The novel solid preparation is suitable, for example, for treating

- acute immunological events, such as sepsis, allergy and graft-versus-host reactions and host-versus-graft reactions
- autoimmune diseases, in particular rheumatoid arthritis, systemic lupus erythrematosus and multiple sclerosis
- psoriasis, atopic dermatitis, asthma, urticaria, rhinitis and uveitis
- type II diabetes
- hepatic fibrosis, cystic fibrosis and colitis
- cancerous diseases, such as lung cancer, leukemia, ovarian cancer, sarcoma, Kaposi's sarcoma, meningioma, intestinal cancer, lymph node cancer, brain tumours, breast cancer, pancreatic cancer, prostate cancer or skin cancer.

The novel solid preparation can also comprise combination packs or compositions, in which the components are juxtaposed and can therefore be administered simultaneously, separately or at graded time intervals to one and the same human or animal body. According to the invention, components 1 and 2 can also be present in juxtaposed, separate medicinal forms, in particular when the spatial dimensions of the medicinal forms make administration more difficult. This applies, in particular, to the oral forms, since elderly patients often have an aversion to large tablets or capsules. It is imperative that the separate, juxtaposed medicinal forms are arranged so that they can be taken at the same time. In this context, different forms, for example a tablet and a capsule, can also be present alongside each other.

The invention furthermore relates to the use of a combination of compounds 1 and 2 for preparing a pharmaceutical which exhibits a hyperadditive increase in the immunosuppressive effect.

The invention furthermore relates to a process for producing the novel preparation, wherein compounds 1 and 2 and a pharmaceutical excipient are processed into a pharmaceutical administration form.

The novel solid preparation can be present as a dosage unit in the form of medicinal forms such as capsules (including microcapsules), tablets (including coated tablets and pills) or suppositories, with it being possible, when capsules are used, for the capsule material to exercise the function of the excipient and the content to be present, for example, as a powder, gel, emulsion, dispersion or solution. However, it is particularly advantageous and simple to prepare oral (peroral) formulations with the two compounds 1 and 2, which formulations comprise the calculated quantities of the active compounds together with each desired pharmaceutical excipient. A corresponding formulation (suppository) for rectal therapy can also be used. Transdermal administration in the form of ointments, creams or oral administration of solutions which comprise the novel preparation, is likewise possible.

In addition to the active compounds, ointments, pastes, creams and powders can also comprise the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, talc, zinc oxide, lactose, silicic acid, aluminum hydroxide, calcium silicate and polyamide powders, or mixtures of these compounds.

The tablets, pills or granulate bodies can be prepared by customary processes, such as compressing, dipping or fluidized bed processes or boiler coating, and comprise excipients and other customary auxiliary substances such as gelatin, agarose, starch (e.g. potato, corn or wheat starch), cellulose, such as ethyl cellulose, silicon dioxide, various sugars, such as lactose, magnesium carbonate and/or calcium phosphates. The coating solution is normally composed of sugar and/or corn syrup and usually also contains gelatin, gum arabic, polyvinylpyrrolidone, synthetic cellulose esters, surface-active substances, plasticizers, pigments and

similar additives corresponding to the state of the art. Any customary flowance agent, lubricating agent or glidant, such as magnesium stearate and mold lubricant can be used for producing the preparations.

Preferably, the preparations are in the form of casing/core tablets or multilayer tablets, with compound 2 being located in the casing or in the core or in a layer, while compound 1 is located in the core or in the casing or in another layer. Compounds 1 and 2 can also be present in delayed-release form, or be adsorbed to release-delaying material or be enclosed in the release-delaying material (for example material of this kind based on cellulose or polystyrene resin, for example hydroxyethyl cellulose). Delayed release of the active compounds can also be achieved by providing the layer in question, or the compartment, with customary coatings which are insoluble in gastric juice.

The dose to be used naturally depends on different factors, such as the living subject (i.e. human or animal) to be treated, age, weight, general state of health, the severity of the symptoms, the disease to be treated, any accompanying diseases, (if present) the nature of the accompanying treatment with other pharmaceuticals, or the frequency of the treatment. In general, the doses are administered several times daily and preferably from once to three times daily. In this context, the quantities of individual active compound which are used are based on the recommended daily dose of the particular individual active compound and should, in the combination preparation, generally be from 10% to 100% of the recommended daily dose, preferably from 20% to 80%, in particular 50%. The appropriate therapy with the novel combinations consequently comprises, for example, the administration of one, two or 3 individual doses of the preparation composed of

1) 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide in a quantity of from 2 to 20 mg, 2 to 19.9 mg, 4.5 to 19.5 mg, 4.85 to 19 mg, 5 to 18 mg, 5 to 15 mg, 5 to 10 mg, 5 to 9.9 mg, 5 to 9.7 or 5 to 9.0 mg and

2) N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide in a quantity of from 0.3% to 50%, preferably of from 0.5% to 20%, in particular of from 0.8% to 15%, particularly preferably of from 1% to 10%, very particularly preferably of from 1% to 5%; in each case based on the content of 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide, and

3) a pharmaceutically tolerated excipient.

The percentage values (%) of compounds 1 and 2 refer in each case to percent by weight.

The quantities of the active components naturally depend on the number of individual doses and also on the disease to be treated. The individual dose can also be composed of several dosage units which are administered simultaneously.

Example 1

Pharmacological tests

Adjuvant-induced arthritis, modification in accordance with Perper (Proc. Soc. exp. Biol. Med. 137, 506 (1971))

Male rats of a Lewis strain (Moellegard, Denmark) having a body weight of from 160 to 210 g are used as the experimental animals. On the 1st day, the animals are injected subcutaneously, into the tail root, with complete Freund's adjuvant containing a suspension of Mycobacterium butyricum in heavy paraffin oil (Difco; 6 mg/kg in paraffin oil; Merck). Compounds 1 and 2 are suspended in carboxymethyl cellulose (1% in water) and this suspension is administered orally. The compounds are administered once daily from the 1st to the 12th day of the experiment. The paw volume and the arthritis index are determined on the 18th day.

The severity of the disorder is determined by measuring the volumes of both hind paws. The measurement is carried out by the water displacement method, using a 2060 plethysmometer (Rhema-Labortechnik, Hofheim, Germany). In addition, the arthritis index is determined on the 18th day after injection.

Determination of the arthritis index:

1.	Ears	0.5 point for each ear on which redness appears and nodules are formed
2.	Nose	1 point for connective tissue swelling
3.	Tail	1 point for the emergence of nodules
4.	Front paws	0.5 point for each paw in which at least one inflammation appears on a joint
5.	Hind paws	1 point for slight inflammation (swelling) 2 points for a medium-strength inflammation 3 points for a massive inflammatory reaction

Animals forming a control group are only given the solvent (1% carboxymethyl cellulose in water). 6 animals are used for each dose and in the control group. A reduction in the increase in paw volume and a decrease in the arthritis index, as compared with the untreated control group, are used as the criteria for an effect having been achieved.

Table 1 shows the results. The total quantity of compounds 1 and 2 is constant in each of the different experiments.

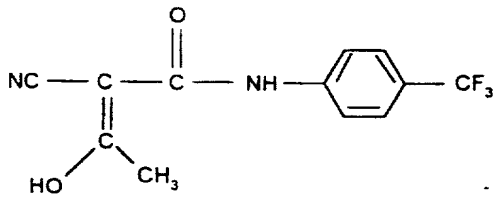
Table 1

Compound 1 (mg/kg of rat)	Compound 2 (mg/kg of rat)	Decrease in paw volume (%)	Decrease in arthritis index (%)
10	0	74	58
9.9	0.1	93	66
9.7	0.3	94	71
9.0	1.0	95	66
5	0	10% increase	12% increase
4.85	0.15	10	5
4.5	0.5	46	35

Both at 5 mg/kg and at 10 mg/kg of rat live weight, the effect of the novel preparation is markedly intensified by increasing quantities of compound 2. Therefore, small additional quantities of compound 2 lead to a marked intensification of the effect of the novel preparation.

Patent claims

1. A solid preparation, comprising
component 1) 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide,
component 2) the compound of formula I



(1)

and/or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I, and
3) a pharmaceutically tolerated excipient,
wherein the content of component 1 is from 2 to 20 mg and the content of component 2) is from 0.3% to 50% of that of component 1).

2. The preparation as claimed in claim 1, wherein the content of component 2) is from 0.5% to 20% of that of component 1).

3. The preparation as claimed in claims 1 or 2, wherein the content of component 2) is from 0.8 to 15% of that of component 1).

4. The preparation as claimed in one or more of claims 1 to 3, wherein the content of component 2) is from 1% to 10% of that of component 1.

5. The preparation as claimed in one or more of claims 1 to 4, wherein the content of component 2) is from 1% to 5% of that of component 1.

6. The preparation as claimed in one or more of claims 1 to 5, which comprises components 1 and 2 in an administration form for rectal or oral administration.

7. The preparation as claimed in one or more of claims 1 to 6, wherein components 1 and 2 are present in similar, separate administration forms for being administered at the same time.

8. The preparation as claimed in one or more of claims 1 to 7, wherein components 1 and 2 are present in separate, different administration forms for being administered at the same time.

9. The use of the preparation as claimed in one or more of claims 1 to 8 for treating immunological diseases.

10. The use of the preparation as claimed in one or more of claims 1 to 8 for treating acute immunological events, such as sepsis, allergy and graft-versus-host reactions or host-versus-graft reactions, or autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythrematosus or multiple scelerosis, or psoriasis, atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis or hepatic fibrosis, or cancerous diseases, such as lung cancer, leukemia, ovarian cancer, sarcoma, Kaposi's sarcoma, meningioma, intestinal cancer, lymph node cancer, brain tumours, breast cancer, pancreatic cancer, prostate cancer or skin cancer.

11. A process for producing the preparation as claimed in one or more of claims 1 to 8, which comprises processing 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide, the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I and/or a stereoisomeric form of the compound of formula I and a pharmaceutical excipient into a pharmaceutical administration form.

Abstract of the disclosure

Combination preparation, comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide

A solid preparation, comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide is suitable for treating immunological diseases.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Combination preparation, comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide and N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide

the specification of which
was filed on March 07, 1997 as International Patent Application PCT/EP97/01167;
on July 14, 1998 as United States Patent Application No. 09/101,672
and was amended on July 15, 1998
I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) for which Priority is Claimed:

Federal Republic of Germany, 19610955.8 of March 20, 1996

And I hereby appoint
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all of the firm of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, Reg.No. 22,540, my attorneys, with full power of substitution and revocation to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therein, and specify that communications about the application are to be directed to the following correspondence address:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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